action. Thus, the examiner has not taken into consideration applicants' amendment of May 20, 2002, which revised independent claims 1, 19, and 24 in view of the examiner's first office action. In particular, applicants have amended the phrase "pharmaceutically acceptable amide of isovaleric acid" to "isovaleramide."

The examiner alleges that Rork *et al.* teaches sustained-release formulations comprising an active agent core and a film coating. The core is made of (a) diethylisovaleramide or bromo-isovaleryl-urea and (b) a polymer that forms gel beads upon hydration and dissolves slowly (specifically, sodium acrylate or carboxymethylene), and the film coating is made of ethyl cellulose or cellulose acetate, *inter alia*.

According to the examiner, the "matrix" of the instant claims reads on Rork's admixture of drug and polymer. The examiner believes, for example, that

> ...Rork teaches diethylisovaleramide and not isovaleramide. However, instant claim 1 recites a pharmaceutically acceptable amide of isovaleric acid, which includes the diethylisovaleramide of Rork.

Again, these remarks are not apropos to applicants' amended claims, as discussed above. In particular, the examiner's assertion that "matrix," as presently recited, reads on the admixture of Rork is inapposite to the amended claims. Moreover, the examiner has acknowledged that Rork does not teach sustained-release formulation of isovaleramide.

Balandrin *et al.* is cited for teaching the use of an isovaleramide tablet, capsule, or drop, for treating CNS disorders. The examiner alleges that the skilled artisan would have been motivated to use the isovaleramide tablets of Balandrin *et al.* in the sustained-release composition of Rork *et al.*, with an expectation of prolonging the therapeutic effects of the compounds taught by Balandrin *et al.*. The examiner alternatively alleges that it would have been obvious to use the sustained-release formulation of Rork *et al.* with the isovaleramide of Balandrin *et al.* in order to provide a sustained-release of isovaleramide for a prolonged treatment of CNS disorders such as anxiety or restlessness.

B. Rork does not evidence motivation for making the claimed combination

A *prima facie* case of obviousness requires, *inter alia*, that the examiner identify evidence of motivation for the skilled artisan to have combined teachings from the prior art, in the manner posited by the examiner. Applicants respectfully submit that the examiner has marshaled no such evidence of motivation here.

The examiner has acknowledged that Rork does not mention isovaleramide. The examiner also admits that Balandrin *et al.* is silent regarding the duration of anxiolytic or sedative effects of isovaleramide, or how long an effect is even desired. Nevertheless, Rork *et al.* is said to suggest using any hypnotic or sedative in a controlled-release formulation; hence, motivation for using isovaleramide, per Balandarin *et al.*, in the formulation of Rork *et al.*

The examiner's extrapolation of Rork *et al.* is unwarranted, however. Rork *et al.* is concerned with a particular type of sustained-release formulation, which he says can be used with *any* "pharmaceutically active agent" (column 5, lines 18-19). Rork *et al.* then uses almost three columns to list, in boilerplate fashion, virtually every conceivable group of "pharmaceutically active agent," as well as some 100 or more specific compounds (column 5, line 27 to column 7, line 20). The class of hypnotics and sedatives is only one of the many compound categories so listed.

Thus, Rork *et al.* gives no effective guidance regarding which compounds might be particularly useful or desirable in the described formulation. Accordingly, one of ordinary skill would have had to pick and choose from the aforementioned list, more or less at random. By the examiner's reasoning, Rork *et al.* renders unpatentable the use of almost any drug in the controlled-release formulation, which is not consistent with a proper obviousness analysis. Such "picking and choosing" is the essence of hindsight analysis.

Moreover, the skilled artisan would not have been motivated to make a sustained-release formulation for a particular compound, absent an identified need to do so:

> The concept of sustained release formulations was developed to eliminate the need for multiple dosage requirements, particularly for those drugs requiring reasonably constant blood levels over a long period of time. In addition, it has been adopted for those drugs that need to be administered in high dosages, but where too rapid a release is likely to cause undesirable side effects (e.g., the ulceration that occurs when potassium chloride is released rapidly in the gastrointestinal tract).

REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 20th ed. at page 898 (appended). In a related vein is the following discussion of "Drug properties relevant to controlled-release formulation":

> The design of controlled-release delivery systems is subject to several variables of considerable importance. Among these are the route of delivery, the type of delivery system, the disease being treated, the patient, the length of therapy, and *the properties of the drug*. Each of these variables is interrelated, and this imposes certain constraints upon choices for the route of therapy, the design of the delivery system, and the length of therapy. *Of particular interest to the scientist designing the system are the constraints imposed by the properties of the drug. It is the properties that have the greatest effect on the behavior of the drug in the delivery system and in the body....*

Id. at page 906, column 2 (emphasis added; excerpts appended). See also the passage on page 908 of REMINGTON (appended), which discusses drug stability:

> Of importance for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract.... *Controlled drug-delivery systems may provide benefits for highly unstable drugs.*

There is nothing in the art of record that implicates any of the considerations, identified by REMINGTON, that would bear on the prospect of incorporating isovaleramide into a sustained-release formulation. Rather, it is applicants' disclosure that elaborates a rationale for making a sustained-release formulation for isovaleramide:

> It has been discovered herein that orally administered isovaleramide has a short half-life in humans. In the absence of an approach to reduce the rate of uptake of drug following administration, the short half-life requires that isovaleramide be administered frequently to sustain a therapeutic concentration of the drug without adverse effects....

(Present application, page 2.) In other words, it was applicants' recognition of

the short half-life of isovaleramide that pointed the way to a sustained-release formulation, as presently claimed.

By the same token, it was applicants' idea and not some notion in the art to apply isovaleramide in treating *chronic* pathological conditions—epilepsy, stroke, bipolar disorder, migraine, anxiety, spasticity, spinal cord injury, chronic neurodegenerative disorder, Parkinson's disease, Huntington's disease, and Alzheimer's—such that prolonged- or sustained-release would be desirable (see application at page 1). The examiner effectively factors this consideration into the analysis only through the exercise of improper hindsight, informed by applicants' own disclosure.

It is submitted, therefore, that applicants' claimed invention is not obvious over any combination of Rork *et al.* and Balandrin *et al.* For this reason alone, withdrawal of the rejection is warranted.

Applicants also submit the declaration of Dr. Manny Balandarin, attesting to the instability and short half-life of isovaleramide, relative to *N,N*-diethylisovaleramide. In particular, Dr. Balandarin has determined that isovaleramide is about twelve times more water-soluble than *N,N*-diethylisovaleramide, an indication that the former is excreted more quickly and has a shorter biological half-life than the former (declaration, ¶ 2).

Conversely, because *N,N*-diethylisovaleramide does not have so short half-life and, hence, would not necessarily be a good candidate for a controlled-release formulation, neither Rork *et al.* or Balandarin *et al.* would have prompted the skilled artisan, without more, to generalize to isovaleramide for purposes of making a controlled-release formulation. Thus, there is evidence of record that further supports the proposition, not presaged in the prior art, that isovaleramide should be an active ingredient for a sustained-release formulation, as presently claimed.

II. The Rejection over Balandrin *et al.* in view of Rork *et al.* and Pankhania *et al.*

Claims 6, 12, 13, 21, and 28 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Rork *et al.*, U.S. Patent No. 5,582,838, in

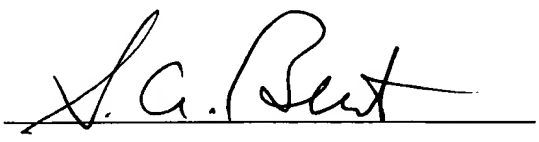
view of Balandrin *et al.*, U.S. patent No. 5,506,268, and further in view Pankhania *et al.*, U.S. patent No. 5,415,871. Pankania *et al.* is alleged to teach xantham gum as a gelling agent in sustained-release formulations for pharmaceutically active agents such as sedatives, and is admittedly not described in Balandrin *et al.* or Rork *et al.* Applicants respectfully traverse the examiner's rejection and submit that the examiner has not made a *prima facie* case of obviousness for the reasons stated above. Balandrin *et al.* and Rork *et al.* do not render obvious the claimed sustained-release formulations because neither specifically suggests the desirability of a sustained-release formulation for the compounds specifically claimed. Pankania *et al.*'s teaching regarding Xantham gum's utility as a gelling agent also does not supply the necessary motivation to make the claimed combination.

It is respectfully submitted that Applicants' claimed invention is not obvious over any combination of Rork *et al.*, Balandrin *et al.*, and Pankania *et al.*, and therefore, withdrawal of this ground for rejection is courteously requested.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Examiner Channavajjala is invited to contact the undersigned if there is any issue that may require further consideration.

Respectfully submitted,

Date April 11, 2003 By 

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